The QT/QS2 Ratio: A Risk-Marker for Torsades De Pointes In Conscious Dogs After IKs-blockade And Beta-Adrenergic Triggers

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Beta-adrenergic stimulation in combination with a diminished ‘repolarisation-reserve’ was applied to induce LQT1-'adrenergic dependent' Torsades de Pointes (TdP) in anaesthetised dogs. The Electromechanical window (EMw) is a recently proposed TdP risk-marker describing the temporal difference between electrical and mechanical events in beating hearts (van der Linde et al., BJP, in press). In clinical situations, the QT/QS2 ratio has been used as an indication for the relationship between the electrical systole (measured by the time between the Q wave and the end of the T wave on the ECG signal; QT interval) and that of the mechanical systole (measured by the time between the Q wave and the second heart sound; QS2).

To investigate if QT/QS2 could be a useful pro-arrhythmic biomarker in conscious dogs, eight beagle dogs (six male and 2 female; body weight between 11.9 to 15.7 kg) were placed in a sling and ECG and heart sounds were measured. Dogs were studied over several days depending on successful induction of TdP (dogs displaying TdP then VF were not recovered by defibrillation). All dogs were treated with a potent IKs blocker (JNJ303; 0.1 mg/kg/min, IV) and after 15 minutes the dogs were triggered with a bolus injection of isoproterenol (0.5 µg/kg, IV) or a more “natural” stimulus (“fright” with an air brush) to induce a beta-adrenergic stimulation and possible induction of TdP. To block the induction of TdP, the L-type calcium blocker verapamil (0.4 mg/kg IV, n = 4) or a beta-blocker atenolol (1 mg/kg IV, n = 4) were given before the adrenergic trigger. After JNJ303 infusion (n = 8) for 10 minutes, QT interval was prolonged (from 216 ms up to 396 ms), QS2 was slightly shortened (from 223 ms down to 201 ms), resulting in a doubling of the QT/QS2 ratio (from 0.98 to 1.99). Four dogs received directly the isoproterenol injection at 15 minutes and showed an increase in heart rate (from 74 b.p.m. up to 148 b.p.m.) and comparable shortening of QT (from 406 ms down to 333 ms) and QS2 (from 201 ms down to 156 ms), resulting in a sustained QT/QS2 ratio of 2.11, and TdP was observed in all four dogs. The four dogs that were pre-treated with verapamil showed no TdP after isoproterenol injection and a low QT/QS2 ratio (1.44), caused by a decreased QT interval (198 ms). The four dogs that were pre-treated with atenolol also showed no TdP after isoproterenol and a low QT/QS2 ratio (1.46) caused by an increase in QS2 (196 ms). In three dogs an air brush stimulus was given during JNJ303 infusion. In all three dogs QT/QS2 ratio was enhanced, T wave morphology changes were noted and R on T events were observed. One dog showed a salvo of TdP and another dog showed sustained TdP.

In conclusion: in conscious slinged dogs JNJ303 prolonged QT, had no effect on QS2, resulting in an enhanced QT/QS2 ratio. High QT/QS2 ratio predicted the induction of TdP after beta-adrenergic stimulation, as observed after isoproterenol, and also after a more “natural” stimulus (“fright” with an air brush).